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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,081	04/05/2006	Olli Vuolteenaho	50635/002001	9413

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
10/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/562,081	VUOLTEENAHO ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/13/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-37,40-44 and 46-61* is/are pending in the application.

4a) Of the above claim(s) *28-37 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-27,46-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other _____

Detailed Action

Status of Application, Amendments, And/Or Claims:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 July 2009 has been entered.

Amendment filed 13 July 2009 is acknowledged. Claims 1-3, 5, 9-11, 18-21, 23, 27, 46-49, 51, 52, 56, 59 and 60 are amended and the amendment made of record. Claim 61 is newly presented and made of record.

Claims 1-21, 23-37, 40-44, and 46-61 are pending in the instant invention. Claims 28-37 and 40-44 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. In the original response to requirement for election of species (Response of 10 July 2008), applicants elected the following species: .SEQ ID NO:3 (NT-proANP), SEQ ID NO:6 (NT-proBNP), SEQ ID NO:9 (polynucleotide encoding SEQ ID NO:3), and SEQ ID NO:12 (polynucleotide encoding SEQ ID NO:6). Claims 1-21, 23-27, and 46-61 are under consideration to the extent they read on the elected invention.

Withdrawn Objections/Rejections

Withdrawn Objections:

The objection to Claim 60 is withdrawn in light of Applicants' amendment to the claims.

Withdrawn Rejections:

The rejection of Claims 18, 19, 23, 24, 49, 50, 56 and 57 under 35 U.S.C. 101 is withdrawn in light of Applicants' amendment to the claims. New issues are set forth below.

The following rejections under 35 U.S.C. 112, second paragraph are withdrawn in light of Applicants' amendment to the claims:

The rejection of Claims 10 and 19 as being unclear as to whether applicants require that there be a single protein or two protein sequences

The rejection of Claims 10 and 19 as vague and indefinite in reciting "the agent comprises or consists of...".

The rejection of Claim 20 as vague and indefinite for not clearly stating how the SEQ ID NOs recited in claim 20 are related to the polypeptides recited in claim 19.

The rejection of Claim 23 as not clearly specifying what "a polypeptide" refers to

The rejection of Claims 47 and 59 as vague and indefinite in reciting "a first binding substance which is able to bind to: (c) (i), (ii), (iii), (iv) ***and/or*** (d) (i), (ii), (iii), (iv).

The rejection of Claim 49 as vague and indefinite in reciting "An agent... which comprises both proANP and proBNP"

The rejection of Claim 52 for not clearly identifying how many sequences (polypeptides) the binding substance is to bind

The rejection of Claim 60 as vague and indefinite in reciting "The method of claim 49"

Remaining and new issues under 35 U.S.C. 112, second are discussed below.

The rejection of Claims 1-6, 9-17, 46-48, 52-55 and 59 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in part, in light of Applicants' amendment to the claims. Issues still remaining are discussed below.

The rejection of Claims 1-6, 9-17, 24, 46-48, 50, 52-55 and 59 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn, in part, in light of Applicants' amendment to the claims. Issues still remaining are discussed below.

The rejection of Claims 18- 22, 49, and 56 under 35 U.S.C. 103(a) as being unpatentable over Nakata et al. (2001. EP1 118 329 A1) in view of Buechler et al (the '838 patent) is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 23-27, 50, 51, 57 and 58 under 35 U.S.C. 103(a) as being unpatentable over Lewicki et al (the '286 patent) and Simari (WO 00/71576, the '576 reference) is withdrawn in light of Applicants' amendment to the claims.

Additionally, any objections or rejections not specifically maintained or presented in this Office Action is hereby withdrawn.

Maintained and/or New Objections and/or Rejections

Objections

Claims:

Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. It is unclear how the recitation of "wherein the fusion polypeptide agent is a peptide" further limits Claim 3 which recites "a fusion polypeptide agent".

Claim 23 is objected to because of the following informalities: The claim contains a typographical error. It is suggested that claim be amended to read "A polynucleotide comprising ***a*** sequence..." or "A polynucleotide comprising ***the*** sequence..." .

Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. It is unclear how claim 48 further limits claim 5, from which it depends, as claim 48 recites the identical limitations recited in Claim 5.

Rejections

35 U.S.C. § 101:

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 26 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim, as recited, reads on host cells, including any eukaryotic cell. There is no limitation wherein the host cells are isolated or in culture; therefore the claim reads on transfected cells in a human, and thus is not patentable subject matter. This rejection could be overcome by adding a limitation wherein the host cells are isolated.

5 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 46-48, 52-55, and 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, an independent method claim of the instant invention, is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps. The claim has been amended to recite "wherein detection of the presence or an increase in the proportionally cumulative amount.... In the sample indicates activation of the ANP and BNP hormonal systems, and detection of a decrease in the proportionally cumulative amount proANP and proBNP ..... in the sample indicates inactivation of these systems". However, the art teaches (See, for example, Clerico et al. 1998, Figure

3, cited in previous office actions) that these peptides are also present in samples from normal individuals. The claim does not recite a step indicating how one skilled in the art can conclude that the levels of the peptides of interest are increased or decreased or that there has been a change in "proportionally cumulative amount" (i.e. is one to compare values to a standard or control from normal individuals?). Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP or a change in the proportional cumulative amounts of the proANP and proBNP in a sample from the subject.

Applicants' traverse this rejection (Response of 13 July 2009, page 2, last paragraph, bridging page 3, first paragraph). The reason for the traversal is that the detecting step recited in the claimed method is sufficient to provide the indication of an increase or decrease to a user of the method. Assay systems can be pre-calibrated so that detection by the system of the mere presence (or absence) of a target, or detection by the system of an amount of a target, is indicative of the desired determination (see, e.g., paragraphs 134 and 315 of the publication of the present application).

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

As indicated above, detecting the presence of the polypeptides of interest would not be sufficient to determine the activation of ANP and BNP hormonal systems, since the polypeptides are present in samples from normal individuals. Applicants have not indicated what level of increase above control would be a positive response. Furthermore, since the term "proportionally cumulative amount" is not defined, one of ordinary skill would be unable to practice the method as described in claim 1 to determine whether activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems has occurred.

Applicants are reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Additionally Claim 1 and newly submitted Claim 61 are vague and indefinite in reciting "proportionally cumulative amount". While the term is recited in the specification [for example, paragraphs 0123, 0144, 0146, 0149, 0155, 0160, 0166, and 0167 of PGPUB 20070141634, the PGPUB of the instant application], there is no definition of the term presented in the disclosure. Thus, one of ordinary skill would be unable to determine how to measure "proportionally cumulative amount".

The rejection of Claims 3 and 47, which depend from Claim 1, under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is maintained for reasons of record. See MPEP § 2172.01. Claim 1 is directed to a method of determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject. Claim 3 recites contacting the sample with a fusion polypeptide agent comprising both proANP and pro-BNP and contacting the sample with a binding substance which is able to bind to pro-ANP and proBNP and a fusion polypeptide comprising both proANP and pro-BNP. One of ordinary skill in the art would be unable to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of contacting the sample with an agent comprising atrial and brain natriuretic peptide prohormones as recited in claim 3. While the claim recites contacting steps, it fails to ***explicitly*** recite method steps directed to **detection** of the atrial and brain natriuretic peptide prohormones that are present in the sample and distinguishing said peptides from the added agent. Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or

inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

Applicants' traverse this rejection (Response of 13 July 2009, page 3, 2nd paragraph). The reason for the traversal is: Claims 3 and 47 depend from claim 1 and merely specify the nature of certain reagents to be used in the method of claim 1. An example of an embodiment of the method of claims 3 and 47 is recited in the specification as including the use of a fusion polypeptide agent as a calibration reagent (see, e.g., paragraphs 134 and 315 of the published application).

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Claims 3 and 47 recite the active method step of contacting the sample with a fusion polypeptide agent and a binding agent. While the specification [paragraphs 0134 and 315] teach that the fusion polypeptide may be a standard to calibrate the assay or a tracer, these limitations are not recited in the claims. The claims recite contacting the sample which comprises the pro-ANP and pro-BNP to be detected with an agent that comprises pro-ANP and pro-BNP. The claims do not require the fusion polypeptide to be labeled or distinguished in any particular manner. There is no method step instructing the artisan how to distinguish the atrial and brain natriuretic peptide prohormones that may be present in the sample in unknown quantities from the added fusion polypeptide which comprises pro-ANP and pro-BNP.

Claim 17 is vague and indefinite. Claim 17 depends from Claim 1. The claim recites that the method is diagnostic of heart failure or monitors the treatment of a cardiac condition. However, the claim fails to correlate changes in levels of pro-BNP and pro-ANP or changes in the proportionally cumulative amount of pro-ANP and pro-BNP with heart failure or monitoring of treatment. Is an increase of levels of pro-BNP and pro-ANP or proportionally cumulative amount of pro-ANP and pro-BNP indicative of heart failure or is the opposite the case? Does an increase of levels of pro-BNP and

pro-ANP or proportionally cumulative amount of pro-ANP and pro-BNP indicate successful treatment or does the opposite indicate successful treatment?

Claim 55 recites the limitation "wherein the homologous sequence of (c) or a fragment thereof that is at least 6 amino acids in length and is capable of binding to a second binding substance, which also binds to the sequence of (a)". The claim depends from Claim 48 which does not have a part (c) nor does it recite a fragment of at least 6 amino acids in length. Therefore, there is insufficient antecedent basis for this limitation in the claim.

The remainder of the claims is included in this rejection as dependent upon a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

It is noted that part of the rejection of the claims under 35 U.S.C. 112, first paragraph (scope of enablement) was withdrawn in the previous Office Action in light of Applicants' arguments. However, upon further consideration and consultation, the Examiner finds that not all of the previously raised issues have been satisfactorily resolved. The rejection is therefore recast and reinstated.

Claims 1-17, 46-48, 52-55 and 59-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining activation of the ANP and BNP hormonal system and using said method to diagnose heart failure or monitor treatment of a cardiac condition, said method comprising simultaneously detecting the presence or amount of atrial and brain natriuretic peptide prohormones or fragments thereof which comprises:

A. Contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance is an antibody or antigen binding fragment thereof

said binding substance being able to bind to

a) (i) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3), (the elected species)

b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) (the elected species) and

c) a fusion polypeptide comprising both (a) and (b)

and comparing the detected amount in the sample to a control or a standard, thereby determining that the amount of said hormones is higher or lower than the control amount,

thereby diagnosing heart failure if the levels of detected polypeptides are increased compared to a control level or thereby monitoring a cardiac condition

or

a method comprising

B. contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance comprises SEQ ID NOs:33 (natriuretic receptor GC-A) or 34 (extracellular binding domain of the natriuretic receptor GC-A) said binding substance being able to bind to both

a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3) (the elected species) and

b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6) (the elected species) and

c) a fusion polypeptide comprising both (a) and (b)

and comparing the detected amount in the sample to a control or a standard, thereby concluding that the amount of said hormones is higher or lower than the controlled amount,

thereby diagnosing heart failure if the levels of detected polypeptides are increased compared to a control level or thereby monitoring a cardiac condition

does not reasonably provide enablement for a method comprising

A. Contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance is an antibody or antigen binding fragment thereof

said binding substance being able to bind to

a homologous sequence having at least 70% identity to a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3), (the elected species) and having at least 70% identity to b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) (the elected species) or

a species homologue or allelic variant of (a) or (b) or

a fragment of (a) or (b) which is at least 6 amino acids in length

or

a method comprising

B. contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance comprises a fragment of SEQ ID NO:33 (natriuretic receptor GC-A) which is at least 400 amino acids in length, said binding substance being able to bind to a homologous sequence having at least 70% identity to a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3), (the elected species) and having at least 70% identity to b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) (the elected species) or

Fragments of (a) or (b) which are at least 6 amino acids in length

Said method diagnosing heart failure if the levels of detected polypeptides are increased compared to a control level or thereby monitoring a cardiac condition

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth

of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

A. The claims are broadly drawn to a method comprising contacting the sample with a binding substance (antibody) that binds to both a sequence of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 or a homologous sequence which has at least 70% identity to SEQ ID NOs:1-3 and a homologous sequence which has at least 70% identity to SEQ ID NOs:4-6 or species homologues or variants or a fragment of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 which is at least 6 amino acids in length and using the results obtained by such a method to diagnose or monitor cardiac disease. One of ordinary skill in the art would be unable to practice this method utilizing a binding substance (antibody) that binds to both a homologous sequence which has at least 70% identity to SEQ ID NOs:1-3 and a homologous sequence which has at least 70% identity to SEQ ID NOs:4-6 or species homologues or alleleic variants of the recited sequences or a fragment of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 which is at least 6 amino acids in length (variant polypeptides) without undue experimentation for reasons to be discussed below.

B. The claims are also broadly drawn to a method comprising contacting the sample with a binding substance of SEQ ID NO:33, which is a natriuretic receptor GC-A, or a fragment of SEQ ID NO:33 which is 400 amino acids in length which binds to both a sequence of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 or a homologous sequence which has at least 70% identity to SEQ ID NOs:1-3 and a homologous sequence which has at least 70% identity to SEQ ID NOs:4-6 or a fragment of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 which is at least 6 amino acids in length and using the results obtained by such a method to diagnose or monitor cardiac disease. Thus, the claims encompass utilizing variant receptors (fragments) as binding substances to bind variant polypeptides and fragments thereof. The claims are not enabled for the full scope of the claims for reasons set forth below.

The claims as recited in Section A above are drawn to utilizing a binding substance which is an antibody or antigen binding fragment thereof to detect

polypeptides of SEQ ID NOs:1-3 and polypeptides of SEQ ID NOs: 4-6 and variants thereof or fragments of said sequences that are at least 6 amino acids in length. The full scope of the claims is not enabled for the following reasons.

The specification teaches polypeptides which are the homologous variants having at least 70% identity to the disclosed sequences and/or the fragments thereof that comprise at least 6 amino acids in length [paragraphs 0108 and 0178 of PGPUB 20070141634, the PGPUB of the instant invention]. The specification also discloses variants may include allelic variants, species homologues and the deletion, modification or addition of groups of amino acids within the protein sequence [paragraph 108], without disclosing an upper limit to the number of deletions, modifications or additions. SEQ ID NO:3 is a polypeptide of 98 amino acid residues; SEQ ID NO:6 is a polypeptide of 76 amino acid residues. One of ordinary skill in the art could prepare the myriad of sequences having this level of identity (at least 70%) or prepare fragments of 6 amino acids in length and prepare a binding substance (such as an antibody) to each of the myriad of variants encompassed by the claims. However, applicants have not taught how to identify which of said variants would retain the structural and physiological characteristics of an ANP or a BNP such that one could correlate the changes in levels of such fragments and variants with the presence or absence of heart failure; one could not predict that detecting changes in the levels of any of the myriad of variants would be indicative of changes in activation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems and would be diagnostic of heart failure or useful in monitoring cardiovascular disease.

It would require undue experimentation to prepare the myriad of sequences that meet the limitations recited in the claims, prepare antibodies that bind to said substances and detect said substances in a sample from a subject and determine if the results of detection of levels of variant fragments is diagnostic of heart failure or monitors the efficacy of treatment of a cardiac condition.

As noted above, the claims recite detection of fragments of SEQ ID NO:3 and 6 at least 6 amino acids in length would be useful in the methods of the instant invention and could be used to diagnose heart failure or monitor the efficacy of treatment..

However, the art teaches that amino acid fragments that are 100% identical to at least 6 amino acid fragments of SEQ ID NOs: 3 or 6 are found in polypeptides that have no relationship to NT-pro-ANP or NT-proBNP polypeptides.

Flashner et al. (1996. Mol Microbiol. 19:985) teaches a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:3 (See results in SCORE and alignment below). The sequence is identified as a sequence present in *E. coli*

```
  Query Match             7.1%;  Score 7;  DB 2;  Length 181;
  Best Local Similarity   100.0%;  Pred. No. 24;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy         83 SALLKSK 89
              |||||||
Db         41 SALLKSK 47
```

Parkhill et al. (2001. Nature 413:848) teaches a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:3 (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in multiple drug resistant *Salmonella enterica*.

```
Query Match             7.1%;  Score 7;  DB 2;  Length 192;
  Best Local Similarity   100.0%;  Pred. No. 26;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy         48 ALSPLPE 54
              |||||||
Db         44 ALSPLPE 50
```

Parkhill et al (2000. Nature 403:665) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in the food-borne pathogen *Campylobacter jejuni*.

```
Query Match             9.2%;  Score 7;  DB 2;  Length 429;
  Best Local Similarity   100.0%;  Pred. No. 25;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy         33 VEQTSLE 39
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              |||||||
Db        106 VEQTSLE 112
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Solomon et al. (1992. Yeast 8:273) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid sequence of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as a part of a polypeptide present in the yeast, *Saccharomyces cerevisiae*.

```
 Query Match             9.2%;  Score 7;  DB 2;  Length 571;
  Best Local Similarity  100.0%;  Pred. No. 32;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          7 GSASDLE 13
              |||||||
Db        563 GSASDLE 569
```

Stover et al (2000. Nature 406:959) teach a sequence comprising a 7 amino acid fragment that is 100% identical to a 7 amino acid fragment of SEQ ID NO:6 of the instant invention (See results in SCORE and alignment below). The sequence is identified as part of a polypeptide of *Pseudomonas aeruginosa,* a major opportunistic pathogen.

```
  Query Match             9.2%;  Score 7;  DB 2;  Length 610;
  Best Local Similarity  100.0%;  Pred. No. 34;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          6 PGSASDL 12
              |||||||
Db        254 PGSASDL 260
```

One of ordinary skill in the art would recognize that fragments of polypeptides of such common pathogens as *E. coli, Salmonella enterica, Campylobacter jejuni*, *Saccharomyces cerevisiae*, or *Pseudomonas aeruginosa* could be present in samples taken from subjects recited in the claims of the instant invention. However, applicants have provided no guidance as to how one of ordinary skill in the art would be able to distinguish from false positives generated by detection of such fragments and detection of unspecified and uncharacterized variants or fragments of at least 6 amino acids in length of NT-pro-ANP or NT-proBNP polypeptides; thus undue experimentation would be required to use the methods of the instant invention as a diagnostic method or to

monitor the efficacy of treatment of cardiac disease as required by the claims of the instant invention.

The claims as recited in Section B above are broadly drawn to utilizing a binding substance which is a natriuretic receptor GC-A (SEQ ID NO:33), or a fragment of said sequence which is 400 amino acids in length and which binds to both a sequence of SEQ ID NOs:1-3 and SEQ ID NOs:4-6 or variants or fragments thereof of at least 6 amino acids in length and using the results obtained by such a method to diagnose or monitor cardiac disease. Thus, the claims encompass utilizing fragments of receptors as binding substances to bind variant polypeptides and fragments thereof. The claims are not enabled for the full scope of the claims for reasons set forth below.

Fragments of natriuretic receptor GC-A of SEQ ID NO:33: The claims recite that said binding substance (receptor) may comprise a polypeptide of SEQ ID NO:33 or a fragment which is at least 400 amino acids in length (Claim 5). However, applicants have only disclosed the extracellular domain of natriuretic receptor GC-A, a sequence of 430 amino acids (SEQ ID NO:34) as a fragment which fits the limitations of the claims and retains the required biological activity, that is binding of a cognate ligand. The disclosure has not taught any additional specific sequences nor has it identified which portions of the natriuretic receptor of SEQ ID NO:33 must be present in order that the required binding activity be retained. The specification has not taught which amino acids are required so that the claimed fragment (of at least 400 amino acids in length) retain the required functional characteristic of binding to its cognate ligand.

Variant Polypeptides: As discussed above, the specification teaches polypeptides which are the homologous or allelic variants having at least 70% identity to the disclosed sequences and/or the fragments thereof that comprise at least 6 amino acids in length. [paragraph 0178 of PGPUB 20070141634, the PGPUB of the instant invention]. However, insufficient guidance is presented as to which portions of the polypeptides must be preserved in order to retain the ability to bind to the binding substance wherein the binding substance is a receptor. One of skill in the art would be aware that specific amino acids must be retained in order to enable the ligand to make

contact and bind to its cognate receptor. However, the specification has not disclosed what portions of the ANP (SEQ ID NO:3, the elected species) and the BNP (SEQ ID NO:6, the elected species) polypeptides which are sequences of 98 and 76 amino acid residues, respectively, must be present to enable binding to the receptor. Applicants have not disclosed any structural requirements for retaining the functional characteristic of binding to the cognate receptor.

The art teaches that protein chemistry is one of the most unpredictable areas of biotechnology. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. With specific reference to the ability of a receptor to bind its cognate ligand: Wang et al (2001. J. Biol Chem. 276:49213-49220) show that a single amino acid determines the lysophospholipid specificity of the SIP1 (EDG1) and LPA1 (EDG2) phospholipdis growth factor receptors (abstract). A single amino acid influences the specificity for S1P or LPA (page 49213, 2nd column, last paragraph). However, Applicants have provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, which fragment of at least 400 amino acids in length (fragment of receptor of SEQ ID NO:33) would retain the required binding activity.

It is noted that Applicants have not responded to the portion of the enablement rejection as applied to a fragment of the natriuretic receptor GC-A (SEQ ID NO:33) which is at least 400 amino acids in length (Response of 13 July 2009, page 5, 2nd and 3rd paragraph); the rejection is thus reiterated and maintained.

Due to the large quantity of experimentation necessary to determine whether the recited binding substance (such as the fragment of the receptor of SEQ ID NO:33)

comprising variant sequences or fragments will bind to polypeptide sequences having 70% identity to the disclosed sequences (SEQ ID NOs 1-6), and whether the detection of such variants or fragments could be used to diagnose heart failure or monitor the treatment of a cardiac condition, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite which variant sequences will be retain the required binding characteristics and which variant sequences would be able to bind to the binding substances, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants have traversed the rejection in responses to previous Office Actions. The reasons for the traversal are:

1. The application describes variants of the binding substance targets, and agents, and that these variants could be made and tested using standard methods in the art (Response of 2 February 2009, page 12, last paragraph bridging page 13, 1st paragraph).

2. With respect to proANP and proBNP related sequences (such as sequences having at least 70% identity to proANP, proBNP, and fragments thereof) to which a first binding substance binds, those of skill in the art could readily prepare sequences having this level of identity, and then prepare a binding substance (such as an antibody) that binds to the sequences. Making antibodies that bind to proteins is standard in the art, and Applicants respectfully submit that undue experimentation would not be required to make such antibodies. As to using them in methods to determine activation or inactivation of ANP and BNP hormonal systems, Applicants submit that the binding substances could readily be tested to determine whether they bind to proANP and proBNP-related sequences in samples in the same manner as binding substances directed against proANP and proBNP sequences that are naturally present in patient samples (Response of 2 February 2009, page 13, 2nd paragraph).

3. Applicants site *Ex Parte Kubin* (BPAI 2007) wherein the Board held that a claim to an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to a reference sequence, and having a particular activity, was enabled. The present case is similar to *Kubin* with respect to the claims specifying variants having a certain level of identity, the advanced state of the art, and the high level of skill in the art. Similar to the decision in *Kubin,* Applicants respectfully submit that obtaining and characterizing variants according to the present claims would have been routine (Response of 2 February 2009, page 14, 1st paragraph)

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

With respect to 1 and 2: As stated above, undue experimentation would be required to construct the myriad of variant sequences and fragments of the ANP and BNP fragments, generate binding substances, such as antibodies and utilize them in the methods of the instant invention to diagnose heart failure or monitor treatment of a cardiac condition. While one can make said variants and generate antibodies and test the binding characteristics of such antibodies, one could not predict that the detection of any one of these numerous variants and fragments would correlate with the presence of heart failure or would be useful in monitoring the efficacy of a therapeutic protocol. Applicants envision the detection of fragments of the polypeptides of interest which are as small as 6 amino acids in length. As indicated above, fragments of 7 amino acids in length identical to those within the proteins of interest have been identified in common pathogenic organisms. One of ordinary skill would predict that antibodies generated to recited fragments of at least 6 amino acids in length would cross react with epitopes in pathogenic organisms, thus resulting in false positives. Applicants have presented no guidance as to how to use the methods to diagnose or monitor treatment in the face of possibility of false positives.

With respect to 3: In contrast to the fact pattern in *Ex Parte Kubin,* the claims under consideration are directed to a **method** of utilizing a myriad of variant polypeptides in a method directed to determination of activation or inactivation of a

hormonal system and utilizing said determination to diagnose a disease or monitor the efficacy of treatment of a disease. While it may not be undue experimentation to construct the myriad variant sequences and fragments and generate substances which bind to said variants and fragments, one would be unable to predict whether detection of any one of these unspecified variants and/or fragments would be indicative of activation or inactivation of the hormonal system; one could not predict that the method detecting such unspecified variants or fragments would be diagnostic of heart failure or could be used to monitor the efficacy of treatment of a heart condition. Thus, testing all of the myriad of variants and fragments encompassed by the claims in the methods of the instant invention to determine the presence of which would be diagnostic of heart failure or useful in the monitoring of efficacy of treatment of a heart condition would constitute undue experimentation.

Written Description

It is noted that part of the rejection of the claims under 35 U.S.C. 112, first paragraph (written description) was withdrawn in the previous Office Action in light of Applicants' arguments. However, upon further consideration and consultation, the Examiner finds that not all of the previously raised issues have been satisfactorily resolved. The rejection is therefore recast and reinstated.

Claims 1-17, 46-48, 52-55 and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are method claims, and are drawn to assays utilizing binding substances which bind to polypeptides of SEQ ID NOs:1-6, homologous sequences having at least 70% identity to SEQ ID NOs 1-6 or fragments thereof of at least 6 amino acids in length (for example, Claims 2-17), species homologues, and allelic variants of

said sequences (for example, Claims 46-48). Additionally, the claims are drawn to methods utilizing binding substances wherein the binding substance comprises a natriuretic receptor of SEQ ID NO:33 or a fragment of SEQ ID NO:33 which is at least 400 amino acids in length. Thus, these claims are drawn to methods utilizing several genera: polypeptides of SEQ ID NOs:1-6, species homologues, allelic variants of said sequences and fragments of at least 6 amino acids in length of said sequences, and a receptor of SEQ ID NO:33 and fragments of SEQ ID NO:33 which are at least 400 amino acids in length.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

With regard to polypeptides of SEQ ID NOs1-6 or variants thereof: the claims require that the variants retain the functional characteristics of binding to a binding substance; said binding substance may be a natriuretic receptor of SEQ ID NO:33. However, the specification does not teach any relationship between the structure of the polypeptides and the function, binding to a binding substance (ie an antibody) or to a receptor of SEQ ID NO:33. The specification discloses a method which detects only one subset of the claimed genus; the method is used to measure serum levels of NT-proANP (SEQ ID NO:3, the elected species) and serum levels of NT-proBNP,(SEQ ID

NO:6, the elected species) (Example 3, paragraph 0318). While the disclosure lists a number of fragments to which the binding substance **may** bind, and teaches that the binding substance may bind to a conserved ring structure of amino acids 7 to 23 of ANP (which is SEQ ID:NO:2) and/or amino acids 10 to 26 of BNP (which is SEQ ID NO:5), the specification has not identified which amino acid residues are required to bind to the receptor of SEQ ID NO:33. Additionally, the claims are drawn to species homologues and allelic variants. The specification fails to describe any such homologues or allelic variants and does not disclose any structure physical and/or chemical characteristics of such allelic variants. There is no disclosed correlation between the unknown allelic variants and the disclosed species of SEQ ID NOs:1-6. While the specification teaches methods of obtaining allelic variants and species homologues [paragraph 0109], possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d916, 927,69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

The only methods taught are those utilizing the claimed genera of peptides of SEQ ID NOs:1-6 or variants thereof are methods utilizing pro-ANP (SEQ ID NO:1), ANP (SEQ ID NO:2), NT-proANP (SEQ ID NO:3, the elected species), proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5) and NT-proBNP (SEQ ID NO:6, the elected species). However, the present claims encompass utilizing almost an infinite number of species that are not further described in the methods of the instant invention.

With regard to a receptor of SEQ ID NO:33 and fragments thereof which are at least 400 amino acids in length:

The claims are drawn to receptors of SEQ ID NO:23 or fragments thereof to bind variant polypeptides. In the absence of teachings as to recognized correlation between structure and function (which amino acids of the receptor are required to bind a cognate ligand and which amino acids of variant polypeptides are required to bind to cognate receptor), one would conclude that the specification does not provide written description

of the claimed genus: a genus of receptors of SEQ ID NO:33 or fragments thereof which are at least 400 amino acids in length.

There are two species of the claimed genus disclosed that is within the scope of the claimed genus, *i.*e. the receptor of SEQ ID NO:33, which is a peptide of 1061 amino acids in length and the extracellular domain of said receptor, SEQ ID NO:34, a peptide of 430 amino acids in length. The disclosure of two species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

Therefore, only methods detecting polypeptides of SEQ ID NOs:1-6 and utilizing receptors of SEQ ID NOs:33 and 34, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 18, 21, 49 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a fusion polypeptide agent of SEQ ID NOs:13-20 or fusion polypeptides comprising both one of (1a) SEQ ID NOs 1-3, or (1b) a homologous sequence having at least 70% identity to one of SEQ ID NOs:1-3 or (1c) a fragment of one of (a) or (b) which is at least 6 amino acids in length

and

one of (2d) SEQ ID NOs 4-6, or (2e) a homologous sequence having at least 70% identity to one of SEQ ID NOs:4-6 or (2f) a fragment of one of (2d) or (2e) which is at least 6 amino acids in length. Thus, the claims are drawn to a myriad of fusion polypeptides which may comprise any of the polypeptides listed in 1a-c fused to any of polypeptides listed in 2 d-f, each component of the fusion polypeptide may comprise an almost infinite number of variants and/or fragments.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., fusion polypeptides of SEQ ID NOs:13-20 or fusion polypeptides comprising 1a-c and 2d-f in any combination, as described in the previous paragraph.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. The claims do not require that the fusion polypeptide possess any particular biological activity; the polypeptides are identified only by a partial structure, that is a polypeptide comprising a sequence at least 70% identity to one of SEQ ID NOs 1-3, and a sequence at least 70% identical to one of SEQ ID NOs 4-6 or a polypeptide comprising a fragment of SEQ ID NOs 1-3 and a fragment of SEQ ID NOs 4-6, said fragment being at least 6 amino acids in length, or any combination of the above components of SEQ ID NOs 1-3 and SEQ ID NOs 4-6, or variants or fragments thereof. There is not any identification of any particular portion of the polypeptide structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

There are 7 species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* SEQ ID NOs 13-20. The disclosure of several disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompasses a myriad of highly variant species comprising variant polypeptides and fragments of said polypeptides that are not further described.

Therefore, only fusion polypeptides comprising the amino acid sequences set forth in SEQ ID NOs:13-20, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 23-26, 50 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides comprising both (1a) SEQ ID NOs:7, 8 or 9 or (1b) a sequence complementary to any of sequences disclosed in (1a), or (1c) a sequence which hybridizes under medium or high stringent conditions to (1a) or (1b), or (1d) a sequence which is degenerate as a result of the genetic code to sequences disclosed in (1a-1c), or (1e) a sequence having at least 70% identity to any of sequences disclosed in (1a-1d), or (1f) a fragment of any of sequences disclosed in 1a-1e wherein said fragment encodes a peptide of at least six amino acids in length;

and

(2g) SEQ ID NOs 10, 11, or 12 or (2h) a sequence complementary to any of sequences disclosed in (2g), or (2i) a sequence which hybridizes under medium or high stringent conditions to (2g) or (2h), or (2j) a sequence which is degenerate as a result of the genetic code to sequences disclosed in (2g-2i), or (2k) a sequence having at least 70% identity to any of sequences disclosed in (2g-2j), or (2l) a fragment of any of sequences disclosed in 2g-2k wherein said fragment encodes a peptide of at least six amino acids in length

The claims are drawn to an almost unlimited number of variant polynucleotides as they recite any combination of the 6 polynucleotides or variants thereof as described in 1a-1f and the 6 polynucleotides or variants thereof as described in 2g-2l

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written

description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a number of genera, i.e., nucleic acids encoding fusion polypeptides, said nucleic acids comprising sequences of SEQ ID NOs 7, 8, or 9 and SEQ ID NOs 10, 11 or 12 or variants or fragments thereof as described in the previous paragraph.

The claims do not require that the nucleic acids encode polypeptides of any particular biological function. Thus, the claims are drawn to genera of nucleic acids that are defined only by sequence identity or hybridization ability.

To provide evidence of possession of the claimed genera, the specification must provide sufficient distinguishing identifying characteristics of the genera. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity or hybridization ability (hybridization under conditions of high or medium stringency). One of ordinary skill in the art would recognize that even under conditions of high stringency, a significant degree of mismatch occurs. Thus, hybridization under high or medium stringency would result in a myriad of nucleic acids which are not further described. Additionally, without a recognized correlation between structure and function, one of ordinary skill would not be able to identify without further testing which of those nucleic acids that hybridize to the recited sequences would also encode a polypeptide that binds to the recited binding substance, particularly the receptor of SEQ ID NO:33. Thus one would not conclude that the applicants are in possession of the claimed genus of nucleic acids.

Therefore only polynucleotides comprising : (1) (a) SEQ ID NOs:7, 8 or 9, (b) sequences complementary to SEQ ID NOs:7, 8 or 9 or sequences which are degenerate as a result of the genetic code to 1 a or b; and (2) (c) SEQ ID NOs: 10, 11 or 12 or (d) sequences complementary to SEQ ID NOs:10, 11 or 12 or sequences which are degenerate as a result of the genetic code to 2 c or d, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Claims 27, 51 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of producing a fusion polypeptide agent comprising both one of (1a) SEQ ID NOs 1-3, or (1b) a homologous sequence having at least 70% identity to one of SEQ ID NOs:1-3 or (1c) a fragment of one of (a) or (b) which is at least 6 amino acids in length

and

one of (2d) SEQ ID NOs 4-6, or (2e) a homologous sequence having at least 70% identity to one of SEQ ID NOs:4-6 or (2f) a fragment of one of (2d) or (2e) which is at least 6 amino acids in length said fragment being at least 6 amino acids in length. Thus, the claims are drawn to a myriad of fusion polypeptides which may comprise any of the polypeptides listed in 1a-c fused to any of polypeptides listed in 2d-f, each component of the fusion polypeptide may comprise an almost infinite number of variants and/or fragments.

Since the full breadth of the claims to the fusion polypeptides lack written description, for reasons discussed above, the full breadth of the claims directed to methods of making said fusion polypeptides also lack written description.

Therefore, only methods of making fusion polypeptides comprising the amino acid sequences set forth in SEQ ID NOs:13-20, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Applicants have traversed the rejection in responses to previous Office Actions. The reasons for the traversal are:

1. The function of the sequences recited in the method claims must bind to the first binding substance in a manner that is similar to or can be compared with the binding of the first binding substance to the corresponding reference sequence (Response of 2 February 2009, page 15, 2nd paragraph).

2. The specification provides information concerning conserved structures of the peptides of the present claims. For example, in paragraph [0179] of the application publication, it is noted that both ANP and BNP include sequences that form a conserved ring structure in the native molecules, and that a binding substance of the invention may bind to such structures (Response of 2 February 2009, page 15, last paragraph bridging page 16, 1st paragraph).

3. The genus of claimed nucleic acid molecules is much smaller than the Examiner acknowledges, because claims 24 and 50 depend from claim 23, which requires that the polynucleotide "encodes a fusion polypeptide agent according to claim 18." There is a well-understood relationship between the sequence of a polynucleotide and the sequence of the polypeptide it encodes. Based on the limitation that the nucleic acid molecules encode a fusion polypeptide agent according to claim 18, it would be readily apparent to those skilled in the art that the Applicants were in possession of the invention at the time the application was filed (Response of 13 July 2009, page 6, 1st paragraph).

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

With respect to 1 and 2: Applicants' claims are drawn to a multitude of sequences. While these sequences are claimed in relationship to a references sequence, Applicants have not disclosed which amino acid residues must be retained for the required function, binding to a binding substance; this is particularly relevant when the binding substance is the receptor of SEQ ID NO:33. Applicants claim fragments comprising as few as 6 amino acid residues which are identical to the referenced sequences. Applicants have described fragments of ANP and BNP

[paragraph 0181]; however one cannot determine if these fragments are representative of the huge, highly variant genus recited in the claims of the instant invention. Applicants have disclosed that one may generate binding substances to the conserved ring structure of ANP and BNP; however, applicants' claims encompass variants and fragments which do not comprise these amino acid fragments. The art teaches these conserved regions would be found, for example, in proANP, the pro-peptide of 126 amino acid residues, and in ANP, the mature atrial natriuretic peptide formed by amino acids 99-126 of the prohormone, but would not be found in NT-proANP, the N-terminal fragment that is cleaved off during processing of the molecule (See, for example, Veale et al. 2000. Bioorganic and Medicinal Chem Let. 10:1949-1952, Figure 1). Thus, the claims encompass a myriad of highly variant structures; applicants have not disclosed sufficient information about structure/function relationships to enable one of ordinary skill to determine that applicants were in possession of the breadth of the polypeptides encompassed by the claims.

With respect to 3: Even with the recited limitation of a polynucleotide that "encodes a fusion polypeptide agent according to claim 18.", the genus recited in claims 23-26, 50 and 57 encompass a myriad of molecules that have not been sufficiently described, since claim 18 is drawn to a genus comprising an almost infinite number of polypeptides, as discussed above. As discussed above, claim 18 encompasses not only polypeptides comprising the discloses sequences (SEQ ID NOs:1-6) but combinations of variants and fragments of said sequences; the fragments may be only 6 amino acids in length. Since the full breadth of the claims to the fusion polypeptides lack written description, for reasons discussed above, the full breadth of the claims to polynucleotides encoding said fusion polypeptides also lack written description.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains Patentability shall not be negatived by the manner in which the invention was made

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 1, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998. J Endoc. Invest 21:170-179), in view of Clerico et al. (2000. Clin. Chemistry 46:1529-1534) is maintained and applied to newly presented claim 61 for reasons of record and for reasons set forth below.

It is noted that Claim 1, one of the independent claims of the instant invention has been amended to recite "simultaneously detecting in a single reading, in a single assay the presence or proportionally cumulative amount of atrial and brain natriuretic prohormones". The claims are drawn to an *in vitro* method comprising simultaneously detecting, in a single reading, in a single assay, the presence or proportionally cumulative amount of atrial and brain natriuretic prohormones (proANP and proBNP) in

a sample, wherein the method comprises an immunoassay (Claim 16) , thereby diagnosing heart failure or monitoring treatment of a cardiac condition (Claim 17); detecting the presence or propotionally cumulative amount of said prohormones is done relative to a reference level (Claim 61). As discussed above, the term "proportionally cumulative amount" is not defined in the specification and is vague and indefinite; the term is thus accorded minimal patentable weight.

Clerico et al (1998) teach measurement of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in plasma of patients with heart failure as an assay method useful in follow-up of cardiac patients (monitoring a cardiac condition) (abstract). The measurements are performed on plasma samples from healthy subjects and patients with chronic cardiomyopathy (page 172, 1st column, 2nd paragraph). The polypeptides were both measured in samples from the same subject (page 174, 1st column, 3rd paragraph and page 175, 2nd column, last paragraph); absent evidence to the contrary, said measurements would constitute simultaneous detection. The measurements were performed using non-competitive immunoradiometric assays (IRMA) (page 172, 1st column, last paragraph bridging page 173, 2nd column, 1st paragraph). The reference teaches utilizing standard solutions comprising known quantities of ANP and BNP to generate standard curves which act as reference values to determine the amount of ANP and BNP in the samples from patient subject (Page 172, 2nd column, 2nd paragraph and page 173, 1st column, 1st paragraph).

Clerico et al (1998) does not teach a method comprising detecting the presence of atrial and brain natriuretic peptide prohormones or fragments thereof. Clerico et al (2000) teach that cardiac natriuretic hormones are a family of related peptides including ANP, BNP and other peptides derived from the N-terminal portion of proANP and proBNP peptide chains (abstract). The reference teaches that the N-terminal prohormones (NT-proANP and NT-proBNP) are present in greater amounts in the plasma than ANP and BNP (Table 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and substitute measurement of proANP and proBNP (as taught by Clerico et al (2000) for the

measurement of ANP and BNP as taught by Clerico et al. (1998). The person of ordinary skill in the art would have been motivated to make these modifications because Clerico et al (2000) teach that the prohormones are present in higher concentrations in the plasma and one of ordinary skill in the art would recognize that these may be measured more easily and accurately. One would reasonably have expected success because methods of measuring said prohormones are outlined by Clerico et al (2000).

Additionally, one of ordinary skill, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays (for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Techniques utilizing immunoassays for simultaneous detection of two polypeptides in a single reading in a single assay were well known at the time of the instant invention, as evidenced by Swartzman et al which teaches simultaneous detection of two cytokines, IL-6 and IL-8 in the same high-throughput multiplexed immunoassay. (See, for evidentiary purposes only, Swartzman et al. 1999. Analytical Biochem. 271:143-151, abstract)

Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.

Applicants traverse the rejection (Response of 13 July 2009, page 7, 3rd paragraph, bridging page 8, 4th paragraph). The reason for the traversal is:

Nowhere does either Clerico (1998) or Clerico (2000) teach or suggest the measurement of the presence or proportionally cumulative amount of proANP and proBNP in a reading, in a single assay.

When considered as a whole, Clerico (1998) provides a rationale for measuring ANP and BNP *separately* as "the data reported in Figure 3 suggest that the BNP assay is more useful than the ANP assay for discriminating between normal subjects and patients with cardiomyopathy even including those with only mild symptoms" (page 176,

column 1). Furthermore, Clerico (2000) states [A]lthough ANP and BNP bind to the same specific receptors, they have different types of metabolism and spectra of biological activity, and their production and secretion may be regulated differently in humans. It has been suggested that there may be different pools of intracellular natriuretic peptides that can respond separately to the same hemodynamic events (e.g., overload for ANP) or to the same pathology-related factors (e.g., cardiac hypertrophy for BNP) (Page 1530, column 1). Applicants argue that based on these statements, Clerico (1998) and Clerico (2000) teach the desirability of distinguishing between ANP and BNP levels and, therefore, teach away from the claimed methods, which require a single reading, in a single assay, showing the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed method recites measuring the cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides) are not recited in the rejected claim(s). Claim 1 recites "detecting the presence ***or*** proportionally culmulative amount of atrial and brain natriuretic peptide prohormones....". (Emphasis added by Examiner). Nowhere does the claim preclude detecting each hormone, individually, in a single reading, in a single assay. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to Applicants' arguments that the Clerico references, taken as a whole, teach the desirability of distinguishing between ANP levels and BNP levels:

The data presented in Figure 3 of Clerico et al (1998) clearly demonstrates that **both** ANP and BNP levels are significantly increased in cardiac patients. The reference teaches "As a whole, cardiac patients showed ANP levels significantly ...higher than those observed in normal subjects. However, because circulating ANP levels tended to

increase with the progression of clinical severity of the disease, some patients with only mild ventricular dysfunction can show ANP levels within the normal range ....while patients with more severe heart failure generally show greatly increased values". (page 174, 1st column, 4th paragraph, emphasis added by Examiner). "Circulating BNP levels increased with the progression of clinical severity of disease, consequently patients with more severe disease showed greatly increased values compared to patients with mild symptoms of disease" (page 174, 2nd column). It is noted that the levels of ANP measured in cardiac patients are never lower than those in normal patients. Thus, while differences in BNP levels may be a better diagnostic indicator of *mild* cardiovascular disease, the reference teaches that both ANP and BNP are greatly elevated in patients with clinical severe disease, such as severe heart failure. One of ordinary skill would conclude that elevated levels of BNP, ANP or both would be diagnostic of heart failure, as recited in claim 17 of the instant invention.

Clerico et al (2000) discusses the possibility of different pools of intracellular natruiretic peptides; but it is unclear how this is relevant to the issue at hand, which is whether the references teach away from the fact that increases in levels of ANP and BNP are found in patients with heart failure, and thus would be diagnostic of heart failure. The reference nowhere teaches that measurement of ANP, BNP or both would not result in useful clinical information. Clerico et al. teach "Several recent studies have underlined the clinical importance to routinely assay CNHs (cardiac natriuretic hormones, including ANP and BNP) for classification, follow-up, and/or prediction of mortality/survival rates of all patients with heart failure" (Page 1533, 1st column, 1st paragraph). "In some studies, the assay for N-terminal proANP1-98 peptides (the elected species of the instant invention) was shown to be equally or even more clinically useful than other CNH assays, whereas in others BNP was found to be the best marker of myocardial involvement." (page 1532, 1st column, 1st paragraph). Thus, taken as a whole, the two references establish that both ANP and BNP levels are elevated in patients with severe heart failure and measuring either or both would provide important clinical information.

The rejection is thus maintained.

Claims 2-4, 7-15, 46, 47, 52-54, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) as applied to claim 1 further in view of Buechler et al (US 7,341,838, filed 19 April 2004, priority claimed to provisional application 60/466,358, filed 28 April 2003, the '838 patent). The teachings of Clerico et al (1998) and Clerico et al (2000) are outlined in detail above. In addition to the teachings above, Clerico et al. (2000) teach competitive assays such as radioimmunoasssays comprising labeled antigens such as ANP and BNP (abstract).

The references, singly or in combination, do not teach the following further limitations:

contacting the sample with a bi- or oligo-specific binding substance that is able to bind to both NT-proANP of SEQ ID NO:3 and NT-proBNP of SEQ ID NO:6 and a fusion polypeptide (Claims 2, 3, 46 and 59),

wherein the fusion polypeptide comprises pro-BNP1-76 (SEQ ID NO:6) and proANP 1-98 (SEQ ID NO:3) (claims 9-11),

wherein the binding substance comprises a bi- or oligo specific binding substace or a mixture of mono-specific binding substances (Claim 4), an antibody that binds to NT-proANP of SEQ ID NO:3 and NT-proBNP (SEQ ID NO:6) (Claims 7 and 8), wherein the first binding substance or agent is labeled and/or immobilized (claim 12) and a method which additionally comprises contacting the sample with a second binding substance which is able to bind to the first binding substance, wherein the second binding substance is labeled or immobilized and wherein a precipitate is formed (claims 13-15)

a method of claim 1 which comprises contacting the sample with a fusion polypeptide comprising both SEQ ID NO:3 and SEQ ID NO:6 and a first binding substance which is able to bind to SEQ ID NO:3 and SEQ ID NO:6 and said fusion polypeptide (Claim 47)

wherein the first binding sequence binds to both a homologous sequence or fragments of proANP and a homologous sequence or fragments of proBNP which are at least 6 amino acids in length (Claim 52)

wherein the homologous sequence or fragment of proANP and the homologous sequence or fragment of proBNP is capable of binding to the binding sequence that binds to SEQ ID NO:3 and SEQ ID NO:6 (claims 53, 54 and 60),

It is noted that the claims have been amended to include the presence of a fusion polypeptide comprising both pro-ANP and pro-BNP (for example, Claims 2, 3, 9-11, 46, 47 and 59). The claims, as discussed above, are vague and indefinite in that they do not clearly indicate how one of ordinary skill would be able to distinguish the atrial and brain natriuretic peptide prohormones that may be present in the sample (which are to be detected) in unknown quantities from the added fusion polypeptide which comprises pro-ANP and pro-BNP. However, reading the claims in light of the teachings in the specification, ("an agent may be used as a standard to calibrate the present assays. The agent may be used as a competing antigen in a competition assay [paragraph 0134]") the Examiner has interpreted these claims to be directed to a non-competitive or a competitive binding assay, such as a radioimmunoassay.

The references do not teach the utilization of a fusion polypeptide as a standard or a competitive antigen. However, as discussed above, Clerico et al. (1998) teach using standards of ANP and BNP in the assays for these natriuretic hormones and also teach radioactively labeled antibodies to said peptides (Figures 1 and 2); Clerico et al (2000) teach competitive radioimmunoassays (abstract) and teach the advantages of measuring the prohormones (pro-NT-ANP and pro-NT-BNP). Since, as discussed above, it would be obvious to measure both pro-ANP and pro-BNP in the same assay to increase the efficiency and reduce the costs of said assays, it would be obvious to one of skill in the art to make a fusion protein so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays detecting both polypeptides in a single assay. One would have a reasonable

expectation of success because methods of making fusion protein are well known in the art.

The '838 patent teaches methods of determining treatment regimen for use in a patient comprising determining the presence of fragments of ANP, BNP and CNP precursor peptides or fragments thereof utilizing immunoassays and correlating the presence or amount of said fragments of ANP and BNP to a disease or prognostic state (column 10, lines 53-67)

The '838 patent also teaches a sequence (SEQ ID NO:3) comprising a segment, amino acids 1-98, which is 99.4% identical to SEQ ID NO:3 of the instant invention and is identified as an ANP precursor, pro-ANP (identified as proANP 1-98 of claim 10) (pro-hormone) (See results in SCORE and alignment below).

Alignment match for SEQ ID NO:3 of the instant invention

```
  Query Match             99.4%;  Score 509;  DB 3;  Length 126;
  Best Local Similarity   99.0%;  Pred. No. 4.6e-52;
  Matches   97;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 60
              ||||||||||||||||||||||||||||||||||||||||:||||||||||||||||||
Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
              ||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
```

It is noted that the one amino acid difference between the sequence as taught by the '838 patent and the instant invention is a conservative amino acid substitution of Aspartic acid for Glutamic acid; one of ordinary skill would predict that this conservative substitution would not effect the biological activity, binding characteristics, or three-dimensional configuration of the protein.

The reference also teaches a sequence, SEQ ID NO:1, comprising a segment, amino acids 1-76 which is 100% identical to SEQ ID NO:6 of the instant invention and is identified as a BNP-precursor molecule (proBNP 1-76 of claim 10) (pro-hormone) (See results in SCORE and alignment below).

Alignment match for SEQ ID NO:6 of the instant invention

```
  Query Match             100.0%;  Score 392;  DB 3;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 4.1e-41;
  Matches   76;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPR 76
              ||||||||||||||||
Db         61 IRGHRKMVLYTLRAPR 76
```

One of ordinary skill in the art would recognize that binding substances or antibodies which recognize polypeptides comprising segments 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively, of the instant invention would recognize the polypeptides of the instant invention. Absent evidence to the contrary, these antibodies would also recognize homologous sequences or fragments of SEQ ID NO:3 and SEQ ID NO:6 (as recited by claims 52-54, 59 and 60). The '838 patent teaches measuring fragments in samples; said fragments could be pro-ANP and pro-BNP (column 15, lines 36-43). The fragments are recognized by antibodies. Said antibodies may comprise bivalent antibodies, comprising two Fab fragments linked by a disulfide bridge at the hinge region (column 16, lines 21-23), thus teaching a bispecific binding substance that binds to proANP and proBNP, as required by claims 2, 3, 7, 46, 47, and 59). The antibodies may be monoclonal antibodies or polyclonal antibodies (column 16, lines 34-39), as required by claim 8. The reference teaches immunoassays comprising a tagged antibody (column 18, lines 24-26), a limitation of claim 12. The reference teaches a pure preparation of the known antigen (pro-ANP and pro-BNP, in the instant assay) is needed in order to standardize the assay (column 18, lines 35-40). The '838 patent teaches immunoassays comprising labeled anti-immunoglobulin antibodies (column 18 lines 53-55), thus meeting the limitations of claims 13 and 14. The reference also teaches "capture" or "sandwich" ELISA assays wherein the antigen-

antibody-2nd antibody complex precipitates (column 18, line 60, bridging column 19, line 3) and radioimmunassays (column 18, lines 32-55).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and Clerico et al (2000) and substitute the polypeptides of SEQ ID NOs: 3 and 1 as taught by the '838 patent for the generic proANP and pro-BNP taught by the Clerico et al (2000) and utilize the antibodies and immunoassays taught by the '838 patent in place of the IRMA assays taught by Clerico et al (1998). The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and one of skill in the art would recognize that one may use bivalent antibodies to bind to different antigens, antibodies directed to the full length sequence would also bind homologous sequences or fragments of said sequences and that different types of immunoassays (RIAs, IRMAs and ELISAs) are art-recognized equivalents. Additionally, as discussed above, one would be motivated to make a fusion polypeptide, as recited in claim 10(d) comprising SEQ ID NOs:3 (proBNP 1-76) and SEQ ID NO:1 (proANP 1-98), sequences taught in the '838 patent, to use as a standard in the assays to detect both pro-ANP and pro-BNP in a single assay so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies. One would reasonably have expected success because the references listed above teach utilizing standards comprising ANP and BNP in the immunoassays, and methods of making fusion proteins and bivalent antibodies for use in diverse immunoassays and methods of practicing different immunoassays are well known in the art. Additionally, although the polypeptide of the prior art (SEQ ID NO:3) differs by one conservative amino acid substitution from the sequence of the claimed invention, one of ordinary skill would recognize, absent evidence to the contrary, that polypeptides comprising said sequence would have the same structural and biological characteristics (for example, binding, and antigenicity) as the polypeptide of the instant invention.

Applicants traverse the rejection (Response of 13 July 2009, page 33, 4th paragraph, bridging page 9, 2nd paragraph). The reasons for the traversal are:

A central feature of the present invention is the detection of the presence or proportionally cumulative amount of both proANP and proBNP-related sequences in a single reading, in a single assay. It would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler (' 838) does not teach or suggest testing for the presence or proportionally cumulative amount of proANP and proBNP-related sequences in a single reading, in a single assay.

Applicant's arguments have been fully considered but are not found to be persuasive.

The reasons for maintenance of the rejection of Claim 1 over both Clerico references are set forth in detail above. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed method recites measuring the cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides) are not recited in the rejected claim(s). Claim 1, one of the independent claims of the instant invention, recites "detecting the presence ***or*** proportionally cumulative amount of atrial and brain natriuretic peptide prohormones....". (Emphasis added by Examiner). Nowhere does the claim preclude detecting each hormone, individually, in a single reading, in a single assay. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays, would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both

proteins simultaneously in the same sample. The '838 patent is cited for teaching specific sequences of pro-ANP and pro-BNP identical to those recited in the claims of the instant invention and reciting details of immunoassays using bispecific antibodies and providing details not taught by the Clerico references.

The rejection is thus maintained.

` The rejection of Claims 5, 6, 48 and 55 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) and Buechler et al (the '838 patent) as applied to Claims 1 and 2 and further in view of Bentivegna et al. (WO 01/79231, the '231 reference) is maintained for reasons of record and for reasons set forth below.

The teachings of Clerico et al (1998), Clerico et al (2000), and the '838 patent are outlined in detail above. The references, singly or combined, do not teach the further limitations of a method wherein the binding substance comprises the natriuretic receptor GC-A (SEQ ID NO:33), as recited in claims 5 and 48 or comprises an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO:34) as recited in claim 6 or wherein the homologous sequence is capable of binding to a second binding substance with also binds to SEQ ID NO:33, as recited in claim 55.

The '231 reference teaches a sequence, SEQ ID NO:3, which is 100% identical to SEQ ID NO:33 of the instant invention. This sequence comprises a domain, the extracellular ligand binding domain, that is 100% identical to SEQ ID NO:34 of the instant invention. The reference identifies the sequence as the human NPR1 (receptor) polypeptide, which is recognized in the art as the natriuretic receptor (NPR-A) which binds both ANP and BNP (See alignments below and results in SCORE).

Alignment match for SEQ ID NO:33 of the instant invention

```
 Sequence 1061 AA;

Query Match             100.0%;  Score 5543;  DB 5;  Length 1061;
Best Local Similarity   100.0%;  Pred. No. 0;
Matches 1061;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;
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```
Qy          1 MPGPRRPAGSRLRLLLLLLLPPLLLLLRGSHAGNLTVAVVLPLANTSYPWSWARVGPAVE 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MPGPRRPAGSRLRLLLLLLLPPLLLLLRGSHAGNLTVAVVLPLANTSYPWSWARVGPAVE 60

Qy         61 LALAQVKARPDLLPGWTVRTVLGSSENALGVCSDTAAPLAAVDLKWEHNPAVFLGPGCVY 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 LALAQVKARPDLLPGWTVRTVLGSSENALGVCSDTAAPLAAVDLKWEHNPAVFLGPGCVY 120

Qy        121 AAAPVGRFTAHWRVPLLTAGAPALGFGVKDEYALTTRAGPSYAKLGDFVAALHRRLGWER 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 AAAPVGRFTAHWRVPLLTAGAPALGFGVKDEYALTTRAGPSYAKLGDFVAALHRRLGWER 180

Qy        181 QALMLYAYRPGDEEHCFFLVEGLFMRVRDRLNITVDHLEFAEDDLSHYTRLLRTMPRKGR 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 QALMLYAYRPGDEEHCFFLVEGLFMRVRDRLNITVDHLEFAEDDLSHYTRLLRTMPRKGR 240

Qy        241 VIYICSSPDAFRTLMLLALEAGLCGEDYVFFHLDIFGQSLQGGQGPAPRRPWERGDGQDV 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VIYICSSPDAFRTLMLLALEAGLCGEDYVFFHLDIFGQSLQGGQGPAPRRPWERGDGQDV 300

Qy        301 SARQAFQAAKIITYKDPDNPEYLEFLKQLKHLAYEQFNFTMEDGLVNTIPASFHDGLLLY 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 SARQAFQAAKIITYKDPDNPEYLEFLKQLKHLAYEQFNFTMEDGLVNTIPASFHDGLLLY 360

Qy        361 IQAVTETLAHGGTVTDGENITQRMWNRSFQGVTGYLKIDSSGDRETDFSLWDMDPENGAF 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 IQAVTETLAHGGTVTDGENITQRMWNRSFQGVTGYLKIDSSGDRETDFSLWDMDPENGAF 420

Qy        421 RVVLNYNGTSQELVAVSGRKLNWPLGYPPPDIPKCGFDNEDPACNQDHLSTLEVLALVGS 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 RVVLNYNGTSQELVAVSGRKLNWPLGYPPPDIPKCGFDNEDPACNQDHLSTLEVLALVGS 480

Qy        481 LSLLGILIVSFFIYRKMQLEKELASELWRVRWEDVEPSSLERHLRSAGSRLTLSGRGSNY 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 LSLLGILIVSFFIYRKMQLEKELASELWRVRWEDVEPSSLERHLRSAGSRLTLSGRGSNY 540

Qy        541 GSLLTTEGQFQVFAKTAYYKGNLVAVKRVNRKRIELTRKVLFELKHMRDVQNEHLTRFVG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 GSLLTTEGQFQVFAKTAYYKGNLVAVKRVNRKRIELTRKVLFELKHMRDVQNEHLTRFVG 600

Qy        601 ACTDPPNICILTEYCPRGSLQDILENESITLDWMFRYSLTNDIVKGMLFLHNGAICSHGN 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 ACTDPPNICILTEYCPRGSLQDILENESITLDWMFRYSLTNDIVKGMLFLHNGAICSHGN 660

Qy        661 LKSSNCVVDGRFVLKITDYGLESFRDLDPEQGHTVYAKKLWTAPELLRMASPPVRGSQAG 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 LKSSNCVVDGRFVLKITDYGLESFRDLDPEQGHTVYAKKLWTAPELLRMASPPVRGSQAG 720

Qy        721 DVYSFGIILQEIALRSGVFHVEGLDLSPKEIIERVTRGEQPPFRPSLALQSHLEELGLLM 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 DVYSFGIILQEIALRSGVFHVEGLDLSPKEIIERVTRGEQPPFRPSLALQSHLEELGLLM 780

Qy        781 QRCWAEDPQERPPFQQIRLTLRKFNRENSSNILDNLLSRMEQYANNLEELVEERTQAYLE 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 QRCWAEDPQERPPFQQIRLTLRKFNRENSSNILDNLLSRMEQYANNLEELVEERTQAYLE 840

Qy        841 EKRKAEALLYQILPHSVAEQLKRGETVQAEAFDSVTIYFSDIVGFTALSAESTPMQVVTL 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 EKRKAEALLYQILPHSVAEQLKRGETVQAEAFDSVTIYFSDIVGFTALSAESTPMQVVTL 900
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Qy        901 LNDLYTCFDAVIDNFDVYKVETIGDAYMVVSGLPVRNGRLHACEVARMALALLDAVRSFR 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 LNDLYTCFDAVIDNFDVYKVETIGDAYMVVSGLPVRNGRLHACEVARMALALLDAVRSFR 960

Qy        961 IRHRPQEQLRLRIGIHTGPVCAGVVGLKMPRYCLFGDTVNTASRMESNGEALKIHLSSET 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 IRHRPQEQLRLRIGIHTGPVCAGVVGLKMPRYCLFGDTVNTASRMESNGEALKIHLSSET 1020

Qy       1021 KAVLEEFGGFELELRGDVEMKGKGKVRTYWLLGERGSSTRG 1061
              |||||||||||||||||||||||||||||||||||||||||
Db       1021 KAVLEEFGGFELELRGDVEMKGKGKVRTYWLLGERGSSTRG 1061
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Alignment match for SEQ ID NO:34 of the instant invention

```
  Query Match             100.0%;  Score 2303;  DB 5;  Length 1061;
  Best Local Similarity   100.0%;  Pred. No. 3.2e-201;
  Matches  430;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GNLTVAVVLPLANTSYPWSWARVGPAVELALAQVKARPDLLPGWTVRTVLGSSENALGVC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         33 GNLTVAVVLPLANTSYPWSWARVGPAVELALAQVKARPDLLPGWTVRTVLGSSENALGVC 92

Qy         61 SDTAAPLAAVDLKWEHNPAVFLGPGCVYAAAPVGRFTAHWRVPLLTAGAPALGFGVKDEY 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         93 SDTAAPLAAVDLKWEHNPAVFLGPGCVYAAAPVGRFTAHWRVPLLTAGAPALGFGVKDEY 152

Qy        121 ALTTRAGPSYAKLGDFVAALHRRLGWERQALMLYAYRPGDEEHCFFLVEGLFMRVRDRLN 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        153 ALTTRAGPSYAKLGDFVAALHRRLGWERQALMLYAYRPGDEEHCFFLVEGLFMRVRDRLN 212

Qy        181 ITVDHLEFAEDDLSHYTRLLRTMPRKGRVIYICSSPDAFRTLMLLALEAGLCGEDYVFFH 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        213 ITVDHLEFAEDDLSHYTRLLRTMPRKGRVIYICSSPDAFRTLMLLALEAGLCGEDYVFFH 272

Qy        241 LDIFGQSLQGGQGPAPRRPWERGDGQDVSARQAFQAAKIITYKDPDNPEYLEFLKQLKHL 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        273 LDIFGQSLQGGQGPAPRRPWERGDGQDVSARQAFQAAKIITYKDPDNPEYLEFLKQLKHL 332

Qy        301 AYEQFNFTMEDGLVNTIPASFHDGLLLYIQAVTETLAHGGTVTDGENITQRMWNRSFQGV 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        333 AYEQFNFTMEDGLVNTIPASFHDGLLLYIQAVTETLAHGGTVTDGENITQRMWNRSFQGV 392

Qy        361 TGYLKIDSSGDRETDFSLWDMDPENGAFRVVLNYNGTSQELVAVSGRKLNWPLGYPPPDI 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        393 TGYLKIDSSGDRETDFSLWDMDPENGAFRVVLNYNGTSQELVAVSGRKLNWPLGYPPPDI 452

Qy        421 PKCGFDNEDP 430
              ||||||||||
Db        453 PKCGFDNEDP 462
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It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) Clerico et al

(2000) and the '838 patent and substitute the receptor taught by the '231 reference, which binds both BNP and ANP for the antibodies which bind BNP and ANP (taught by Clerico et al (1998), Clerico et al (2000) and the '838 patent) in the methods of the instant invention. The person of ordinary skill in the art would have been motivated to make these modifications and reasonably have expected success because one of ordinary skill in the art would recognize that both receptors comprising extracellular ligand binding domains and antibodies may be used to bind antigens (or ligands) such as ANP and BNP and would thus be art accepted equivalents.

Applicants traverse the rejection (Response of 13 July 2009, page 9, 3rd paragraph bridging page 10, 1st paragraph).

The reasons for the traversal are:

None of the cited references, alone or in combination, provide any teaching or suggestion of a central feature of the present invention, in which a single assay provides a single reading indicating the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing the individual levels of proANP and proBNP in the sample. Rather, in carrying out methods according to the cited references, those skilled in the art would utilize an assay that *distinguishes* between proANP and proBNP-related sequences.

Applicant's arguments have been fully considered but are not found to be persuasive.

The reasons for maintenance of the rejection of Claim 1 over both Clerico references are set forth in detail above. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed method recites measuring the cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides) are not recited in the rejected claim(s). Claim 1, one of the independent claims of the instant invention, recites "detecting the presence ***or*** proportionally culmulative amount of atrial and brain natriuretic peptide prohormones....". (Emphasis added by Examiner). Nowhere does the claim preclude detecting each hormone,

individually, in a single reading, in a single assay. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays, would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample. The '231 reference is cited for teaching specific sequences of the natriuretic receptor and the extracellular binding domain of said receptor identical to those recited in the claims of the instant invention (Claim 5 and 6).

The rejection is thus maintained.

Claims 18-21, 27, 51, 49, 56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnett et al (US 6,818,619, filed 26 March 2002, the '619 patent) in view of Buechler et al (the '838 patent). The claims are drawn to a fusion polypeptide comprising ANP and BNP or variants thereof and methods of making such polypeptides recombinantly.

The '619 patent teaches natriuretic peptides (NP) which include ANP, CNP, BNP or DNP, portions of a NP, variants of a NP or chimeras thereof (column 5, lines 27-29). The reference specifically describes a chimeric polypeptide comprising BNP with DNP (column 2, line 66, bridging column 3, line 1. The reference also teaches a chimeric rotein, VNP, which comprises ANP and CNP (column 2, lines 16-19). Thus, the reference teaches chimeric proteins comprising natriuretic peptides or variants thereof. The '619 patent teaches that said chimeric peptides have combined effects in vivo, which includes vasodilation, natriuresis and suppression of rennin (column 3, lines 59-61), and thus would be valuable as therapeutic polypeptides. The reference teaches

said chimeric proteins may be prepared by using recombinant DNA based technology (column 10, lines 37-39). Recombinant DNA can be readily introduced into the host cell so that the DNA molecules are expressed by the host cell (column 13, lines 46-55) and the protein thus produced.

While the '619 patent does not teach a chimeric protein specifically comprising ANP and BNP, the reference does teach specific chimeric proteins comprising each individual protein fused to second natriuretic polypeptide. Additionally, the reference teaches chimeric peptides comprising any of four identified natriuretic polypeptides. Thus, it would be obvious to the person of ordinary skill in the art at the time the invention was made to modify the specific fusion proteins taught by the '619 patent which comprise BNP and DNP or ANP and CNP and construct a fusion protein comprising ANP and BNP. One of ordinary skill in the art would be motivated to make such a fusion protein and would anticipate success because the '619 patent teaches chimeric natriuretic peptides may comprise ANP, CNP, BNP or DNP, portions of a NP, or variants of a NP and teaches the therapeutic advantages of such chimeric polypeptides; furthermore, methods of making fusion proteins are well known in the art, and are taught by the '619 patent.

Additionally, under KSR, it is now apparent "obvious to try" may be an appropriate test in many situations. Where there is motivation to solve a problem, in the instant case, producing a therapeutic polypeptide with combined effects of two natriuretic polypeptides and there are a finite number of identified, predictable solutions, in the instant case, a maximum of 12 possible polypeptides, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. The fact that a combination was obvious to try might show that it was obvious under 103. KSR Int'lCo. V. Teleflex Inc,. 127 S. Ct. 1727. 82 USPQ2d 1385, 1397 (2007).

The '619 patent does not teach a fusion polypeptide agent comprising any of the components as recited in claims 18-20. Specifically, the '619 patent does not teach a

fusion polypeptide agent comprising a fusion polypeptide agent comprising proBNP1-108 and proANP1-126 (Claim 19(f)) which comprises SEQ ID NO:19 (Claim 20).

The '838 patent teaches polypeptides which comprise sequences comprising segments that are 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively (See alignment above). The '838 patent also teaches sequences comprising proBNP1-108 (SEQ ID NO:1 disclosed in the '838 patent) and a proANP1-126 (SEQ ID NO:3 disclosed in the '838 patent) (See results in SCORE); said polypeptides are recited as components of the fusion polypeptide recited in claim 19(f); the recited components comprise SEQ ID NO:19 as recited in claim 20 (See alignments below).

Alignment match for amino acids 1-108 of SEQ ID NO:19 of the instant invention (Claims 19f and 20)

```
  Query Match             45.9%;  Score 561;  DB 3;  Length 108;
  Best Local Similarity  100.0%;  Pred. No. 3.6e-49;
  Matches  108;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
              ||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
```

Alignment match for amino acids 109-234 of SEQ ID NO:19 of the instant invention (Claims 19f and 20).

```
  Query Match             53.9%;  Score 659;  DB 3;  Length 126;
  Best Local Similarity   99.2%;  Pred. No. 4.6e-59;
  Matches  125;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        109 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 168
              ||||||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy        169 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 228
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 120

Qy        229 CNSFRY 234
              ||||||
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Db 121 CNSFRY 126

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '619 patent which teaches generic chimeric polypeptides comprising ANP and BNP and substitute the polypeptides comprising segments of SEQ ID NOs: 3 and 1 or sequences comprising proBNP1-108 and proANP1-126 as taught by the '838 patent for the generic ANP and BNP as taught by the '619 patent. The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and the '619 patent teaches chimeric proteins comprising natriuretic polypeptides such as ANP and BNP variants. Additionally, it would be obvious to one of skill in art to make a fusion protein comprising proBNP1-108 and proANP1-126 comprising SEQ ID NO: 1 and SEQ ID NO:3 taught by the '858 protein to arrive at a fusion protein of SEQ ID NO:19 of the instant invention, which comprises as amino acids 1-108 a sequence which is 100% identical to SEQ ID NO:1 of the referenced patent and as amino acids 109-234 a sequence which is 99.2% identical to SEQ ID NO:3 of the referenced patent. The one amino acid difference comprises the conservative substitution of aspartic acid for glutamic acid (both being acidic amino acids; one of skill in the art would predict that this would not change the biological activity of the fusion protein. One would be motivated to make said fusion protein because the '619 patent teaches the advantages of a therapeutic peptide comprising two natriuretic peptides. One would have a reasonable expectation of success because methods of making fusion proteins are well known in the art.

Claims 23-26, 50, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnett et al (the '619 patent) in view of Buechler et al (the '838 patent) as applied to claim 18 further in view of Lewicki et al (the '286 patent) and Simari (WO 00/71576, the '576 reference).

The teachings of the '619 patent and the '838 patent are outlined in detail above. The two references, individually or in combination, do not teach a polynucleotide

encoding an ANP-BNP fusion protein or a polynucleotide comprising both SEQ ID NOs 9 and 12 (as recited in claim 24) or expression vectors and host cells comprising said polynucleotides.

It is noted that the '619 patent teaches chimeric proteins may be prepared by using recombinant DNA based technology (column 10, lines 37-39) and teaches expression cassettes comprising a DNA encoding chimeric natriuretic peptides (column 12, lines 14-19).

The '286 patent teaches a sequence, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention (See alignment below and results in SCORE). The '286 patent teaches this nucleotide sequence as encoding an atrial natriuretic peptide. The reference teaches expression vectors (for example, column 6, lines 3-18, column 71, line 25) host cells (column 82, lines 46-54), and methods of making the protein of interest recombinantly (column 13, lines 38-42, and column 82, lines 46-54).

Alignment match for SEQ ID NO:9 of the instant invention

```
  Query Match             100.0%;  Score 294;  DB 2;  Length 702;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-86;
  Matches  294;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         32 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 91

Qy         61 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         92 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 151

Qy        121 CCGAATGAAGAAGCGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        152 CCGAATGAAGAAGCGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 211

Qy        181 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        212 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 271

Qy        241 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 294
              ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        272 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 325
```

The '576 reference teaches a sequence that is 100% identical to SEQ ID NO:12 of the instant invention (See alignment below and results in SCORE). This sequence is described as encoding a natriuretic peptide, BNP, useful to inhibit or prevent heart failure. The reference teaches plasmids (page 7, 5th paragraph, Figure 3) and host cells expressing the protein of interest and methods of isolating recombinantly produced protein (page 7, 6th paragraph, Figure 4)

Alignment match for SEQ ID NO:12 of the instant invention

```
  Query Match             100.0%;  Score 228;  DB 4;  Length 330;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-49;
  Matches  228;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          4 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 63

Qy         61 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         64 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 123

Qy        121 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        124 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 183

Qy        181 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 228
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db        184 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 231
```

. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '619 and '838 patents which teach a chimeric protein comprising ANP and BNP and expression cassettes comprising polynuclotides encoding said chimeric or fusion proteins and substitute the polynucleotide taught by the '286 patent, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention, encoding an ANP, for the generic polynucleotide encoding ANP (as taught by the '619 patent) and substitute the polynucleotide sequence taught by the '576 reference comprising a sequence that is 100% identical to SEQ ID NO:12 of the instant invention, encoding a BNP for the generic polynucleotide encoding BNP (as taught by the '619 patent). The person of ordinary skill in the art would have been motivated to make these modifications because

the '619 patent teaches expression cassettes comprising polynucleotides encoding chimeric natriuretic polypeptides and teaches the therapeutic advantages of such polypeptides and the '286 patent and the '576 reference teaches specific polynucleotides encoding ANP and BNP. One would anticipate success because the '619 patent teaches making such expression cassettes comprising recombinant DNA sequences.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Examiner, Art Unit 1647